Measures of Neuronal Response Based on Nonparametric Tests*

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Abstract. Two response indices characterizing the stimulus effect on spontaneously active neurons are developed. They are based on a non-parametric comparison of interspike interval distributions under the spontaneous and the stimulus condition. The response indices obtained with repeated stimuli can be combined into a single multiple-trial index. The method is tested both with different types of simulated spike activity and with actual single unit activity recorded from an auditory centre of a songbird.

1. Introduction

Single unit recordings have proved to be one of the major tools of Brain Research. The analysis of these, however, suffers from severe defects. Only the basic question as to whether the stimulus affects the observed neuronal activity, the question of response detection, seems to be answerable to a satisfactory degree. Since we do not know the functional interconnection of the neuron under study to other neurons any question as to what the observed change in activity means for the nervous system obviously has no chance of solution. For the same reason, scaling of response strength can only be based on our human measures, guided to some extent by our knowledge about simple, peripheral nervous systems.

Nevertheless, the systematic use of available methods and equipment could improve the response analysis methods which are actually applied by most brain researchers. Standard methods (review: Glaser and Ruchkin, 1976) are spike pattern displays (dot display, spike raster), spike counts per stimulus, and the peristimulus time histogram PSTH. The dot display gives merely a stimulus-related image of the original spike train for a number of stimulus repetitions. The two latter methods provide an initial means by which a stimulus effect can be judged with statistical significance. The necessary statistical tests, however, are rarely applied, the main reason being that conditions on which they depend are not met, e.g. a large number of spikes.

Microelectrode recordings from single neurons only last for a limited time, depending on the recording site and the recording technique. Since the response characteristics may differ greatly even among neighbouring neurons all efforts should be undertaken to improve the quantity and quality of the data sampled from a single cell. This seems possible with computer control of the experiment and on-line response analysis. Good on-line strategies should as far as possible avoid the time consuming repetitions of stimuli on which the standard methods depend. They require statistically founded response measures, evaluated on-line on a trial-by-trial basis.

The aim of the present study is to develop such measures and to test them by using computer simulated responses as well as actual single unit recordings. The latter are selected from a current study of central auditory neurons in a songbird. Neurons from this area show complex responses to artificial and natural test sounds (Leppelsack, 1974; Leppelsack and Vogt, 1976). A quantitative response analysis is often difficult due to the low number of spikes involved.

Aspects specially related to applications in on-line controlled experiments will be discussed in later publications.

2. Single Run Response Measures

2.1. Fundamentals

In the following it is assumed that an investigator observes a spontaneously active neuron by extracellular recording techniques. Thus, all information about
the neuron's activity is comprised of a temporal sequence of spikes, or, more specifically, of their occurrence times. In terms of the theory of stochastic processes the occurrence times form a point process (Cox and Lewis, 1966). Each kind of response to a stimulus can be understood as a significant change in the temporal structure of this process after the onset of the stimulus. An unknown period after the stimulus' end the process is expected to return to its undisturbed form.

To evaluate a measure of response from a single trial we have to compare the spike train within a time window where we presume a response with spike data obtained from a stimulus-free “spontaneous” section of the recording. In the following these time windows are called the response window RW and the comparison window CW. If not otherwise stated we will assume that the RW duration $D_r$ is chosen shorter than the duration $D_c$ of the comparison window.

The idea governing the development of the response indices described here is to link the strength of a response to the degree of statistical significance (i.e. “a strong response is a highly significant response”). Following this approach a response index can be achieved in the form of a test statistic of an adequate test of significance. For this test the case of no response is identical to the null hypothesis (NH) stating that the spike sequences observed in both windows are independent samples taken from the same stochastic point process. In the following, two different alternative hypotheses (AH) are stressed, one (AH1) which weights all differences from NH, the other (AH2) being more sensitive to unidirectional differences corresponding to tonic activation or suppression of neuronal activity.

The basic use of a response index, response detection, is facilitated if the probability limits separating response from random are fixed. Therefore, the test statistic should show a null distribution (i.e. under NH) which is independent from additional parameters like spike counts. The following chapters describe the construction of two tests corresponding to the two alternative hypotheses. Their test statistics $p$ (AH1) and $q$ (AH2) are characterized by

1. $0 \leq p \leq 1$, $-1 \leq q \leq 1$,
2. uniform null distributions in these ranges,
3. accumulation near $p = 1$ and $|q| = 1$ with increasing differences from NH, the sign of $q$ indicating excitation (+) or suppression (−).

Obviously, both $p$ and $q$ can be used as response indices. For instance, under the null hypothesis a value $p \geq 0.98$ will appear with probability 0.02. If such a high $p$ value results from spike train analysis it can be taken as an indicator of response with a small error probability $\alpha = 0.02$. With $p$ approaching its upper limit, $p = 1$, the error probability tends to zero. According to the relation set between response strength and significance, $p = 1$ indicates maximum response. An analogue interpretation holds for the absolute value of $q$.

The accumulation of significant responses in the nearest neighbourhood of $p = 1$ and $|q| = 1$ makes their adequate graphical representation difficult. In linear plots strong responses cannot be distinguished from one another and are not sufficiently separated from non-significant values. Therefore it has proven preferable to plot $p^3$ and $q^3$ or other monotonously increasing functions of the response indices.

2.2. Derivation of Response Indices

The derivation of the response indices can be divided into four steps. They are treated in the following subchapters.

2.2.1. Description of Spike Sequences. A large number of point processes have been discussed in the literature (see, for instance, Cox and Lewis, 1966; Snider, 1975), also with respect to single neuron activity (review: Fienberg, 1974). In the present case, the choice of the model used for the description of spike sequences is heavily restricted by the fact that a response is usually reflected by a relatively short alteration of the spontaneous discharge. Thus, all parameters of the model have to be estimated by statistical methods from only few spikes observed in the short response window (RW). This excludes the application of refined models.

On the other hand, the model should at least be able to express the main differences observed in spontaneous spike trains, especially regular and random behaviour. This excludes the description by “mean spike rates” or other averages. As a compromise, a description by a renewal process (Cox, 1962) is adopted. Applied to spike trains, a renewal process is fully characterized by the probability distribution of the interspike intervals (ISI).

Estimation of the ISI distribution requires at least one spike falling into the sampling period (RW or CW; see Appendix 1). Its result is represented by the Empirical Distribution Function (EDF)

$$S(T) = \frac{\text{No. of intervals with length } \leq T}{\text{Total no. of intervals}}$$

wherein the set of intervals is enlarged by one pseudo interval estimated from the open intervals at the boundaries of the time window. For the remainder of this chapter (2.2) it is assumed that $S(T)$ exists both for RW and CW. Spikeless time windows are treated in Appendix 2.

2.2.2. Measuring Distribution Differences. To test for differences between the distribution of two continuous